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(54) Title: CARBOLINE DERIVATIVES AS PDEV INHIBITORS

(57) Abstract: Selective inhibitors of cGMP-specific PDE, and use of the compounds and salts and solvates thereof as therapeutic agents, are disclosed.



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CARBOLINE DERIVATIVES AS PDEV INHIBITORS

FIELD AND BACKGROUND OF THE INVENTION

5 This invention relates to a series of compounds, to methods of preparing the compounds, to pharmaceutical compositions containing the compounds, and to their use as therapeutic agents. In particular, the invention relates to compounds that
10 are potent and selective inhibitors of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP-specific PDE), in particular PDE5, and have utility in a variety of therapeutic areas where such inhibition is considered beneficial, including the
15 treatment of cardiovascular disorders and erectile dysfunction.

SUMMARY OF THE INVENTION

20 The present invention is directed to numerous β -carboline compounds that are potent and selective inhibitors of PDE5. In addition to the compounds specifically disclosed herein, the selective PDE5 inhibitors can contain additional optional
25 substituents.

 For example, in addition to alkyl substituents disclosed herein, the "alkyl" group can be straight chained and branched hydrocarbon groups containing the indicated number of carbon atoms,
30 typically methyl, ethyl, and straight chain and branched propyl and butyl groups. The hydrocarbon group can contain up to 16 carbon atoms. The term "alkyl" includes "bridged alkyl," i.e., a C₆-C₁₆

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bicyclic or polycyclic hydrocarbon group, for example, norbornyl, adamantyl, bicyclo[2.2.2]octyl, bicyclo[2.2.1]heptyl, bicyclo[3.2.1]octyl, or decahydronaphthyl, and "cycloalkyl," i.e., a cyclic C₃-C₈ hydrocarbon group, e.g., cyclopropyl, cyclobutyl, cyclohexyl, and cyclopentyl.

Likewise, a disclosed "aryl" group can be unsubstituted or substituted, for example, with one or more, and in particular one to three, halo, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, haloalkyl, nitro, amino, alkylamino, acylamino, alkylthio, alkylsulfinyl, and alkylsulfonyl. Examples of additional aryl groups include naphthyl, tetrahydronaphthyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methylphenyl, 4-methoxyphenyl, 3-trifluoromethylphenyl, 4-nitrophenyl, and the like.

A disclosed "aryl" group also can be a "heteroaryl" group, unsubstituted or substituted, for example, with one or more, and in particular one to three, substituents, like halo, alkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, haloalkyl, nitro, amino, alkylamino, acylamino, alkylthio, alkylsulfinyl, and alkylsulfonyl. Examples of heteroaryl groups include thienyl, furyl, pyridyl, oxazolyl, quinolyl, isoquinolyl, indolyl, triazolyl, isothiazolyl, isoxazolyl, imidazolyl, benzothiazolyl, pyrazinyl, pyrimidinyl, thiazolyl, and thiadiazolyl, and similar monocyclic and bicyclic ring systems containing one or two aromatic rings, and containing at least one nitrogen, oxygen, or sulfur atom in an aromatic ring.

A disclosed aliphatic heterocyclic can be a heterocycle, termed "Het," which is defined as

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monocyclic, bicyclic, and tricyclic groups containing one or more heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur, optionally containing an oxo group (=O) attached to the ring. Nonlimiting examples of Het groups include 1,3-dioxolane, 2-pyrazoline, pyrazolidine, pyrrolidine, piperazine, a pyrroline, 2H-pyran, 4H-pyran, morpholine, thiopholine, piperidine, 1,4-dithiane, and 1,4-dioxane.

Compounds of the present invention can contain one or more asymmetric center, and, therefore, can exist as stereoisomers. The present invention includes both mixtures and separate individual stereoisomers of the compounds of the present invention. Compounds of the present invention also can exist in tautomeric forms, and the invention includes both mixtures and separate individual tautomers thereof.

Pharmaceutically acceptable salts of the compounds of the present invention can be acid addition salts formed with pharmaceutically acceptable acids. Examples of suitable salts include, but are not limited to, the hydrochloride, hydrobromide, sulfate, bisulfate, phosphate, hydrogen phosphate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, tartrate, gluconate, methanesulfonate, benzenesulfonate, and p-toluenesulfonate salts. The compounds of the present invention also can provide pharmaceutically acceptable metal salts, in particular alkali metal salts and alkaline earth metal salts, with bases. Examples include the sodium, potassium, magnesium, and calcium salts.

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Compounds of the present invention are potent and selective inhibitors of cGMP-specific PDE5. Compounds of the present invention are of interest for use in therapy, specifically for the treatment of a variety of conditions where selective inhibition of PDE5 is considered to be beneficial.

Phosphodiesterases (PDEs) catalyze the hydrolysis of cyclic nucleotides, such as cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). The PDEs have been classified into at least seven isoenzyme families and are present in many tissues (J.A. Beavo, *Physiol. Rev.*, 75, p. 725 (1995)).

PDE5 inhibition is a particularly attractive target. A potent and selective inhibitor of PDE5 provides vasodilating, relaxing, and diuretic effects, all of which are beneficial in the treatment of various disease states. Research in this area has led to several classes of inhibitors based on the cGMP basic structure (E. Sybertz et al., *Expert. Opin. Ther. Pat.*, 7, p. 631 (1997)).

The biochemical, physiological, and clinical effects of PDE5 inhibitors therefore suggest their utility in a variety of disease states in which modulation of smooth muscle, renal, hemostatic, inflammatory, and/or endocrine function is desirable. The compounds of the present invention, therefore, have utility in the treatment of a number of disorders, including stable, unstable, and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, acute respiratory distress syndrome, acute and chronic renal failure, atherosclerosis, conditions of re-

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duced blood vessel patency (e.g., postpercutaneous transluminal coronary or carotid angioplasty, or post-bypass surgery graft stenosis), peripheral vascular disease, vascular disorders, such as
5 Raynaud's disease, thrombocythemia, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, osteoporosis, preterm labor, benign prostatic hypertrophy, peptic ulcer, male erectile dysfunction, female
10 sexual dysfunction, and diseases characterized by disorders of gut motility (e.g., irritable bowel syndrome).

An especially important use is the treatment of male erectile dysfunction, which is one form
15 of impotence and is a common medical problem. Impotence can be defined as a lack of power, in the male, to copulate, and can involve an inability to achieve penile erection or ejaculation, or both. The incidence of erectile dysfunction increases with
20 age, with about 50% of men over the age of 40 suffering from some degree of erectile dysfunction.

In addition, a further important use is the treatment of female sexual arousal disorder. Female sexual arousal disorders are defined as a
25 recurrent inability to attain or maintain an adequate lubrication/swelling response of sexual excitement until completion of sexual activity. The arousal response consists of vasocongestion in the pelvis, vaginal lubrication, and expansion and
30 swelling of external genitalia.

It is envisioned, therefore, that compounds of the present invention are useful in the treatment of male erectile dysfunction and female

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sexual arousal disorder. Thus, the present invention concerns the use of compounds of the present invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing
5 either entity, for the manufacture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal and sexual arousal disorder in a female animal, including humans.

10 The term "treatment" includes preventing, lowering, stopping, or reversing the progression or severity of the condition or symptoms being treated. As such, the term "treatment" includes both medical therapeutic and/or prophylactic administration, as appropriate.

15 It also is understood that "a compound of the present invention," or a physiologically acceptable salt or solvate thereof, can be administered as the neat compound, or as a pharmaceutical composition containing either entity.

20 Although the compounds of the invention are envisioned primarily for the treatment of sexual dysfunction in humans, such as male erectile dysfunction and female sexual arousal disorder, they also can be used for the treatment of other disease
25 states.

A further aspect of the present invention, therefore, is providing a compound of the present invention for use in the treatment of stable, unstable, and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, chronic obstructive
30 pulmonary disease, malignant hypertension, pheochromocytoma, congestive heart failure, acute respiratory distress syndrome, acute and chronic

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renal failure, atherosclerosis, conditions of reduced blood vessel patency (e.g., post-PTCA or post-bypass graft stenosis), peripheral vascular disease, vascular disorders such as Raynaud's disease, thrombocytopenia, inflammatory diseases, prophylaxis of myocardial infarction, prophylaxis of stroke, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, osteoporosis, peptic ulcer, postpercutaneous transluminal coronary angioplasty, carotid angioplasty, preterm labor, benign prostatic hypertrophy, male and female erectile dysfunction, or diseases characterized by disorders of gut motility (e.g., IBS).

According to another aspect of the present invention, there is provided the use of a compound of the present invention for the manufacture of a medicament for the treatment of the above-noted conditions and disorders.

In a further aspect, the present invention provides a method of treating the above-noted conditions and disorders in a human or nonhuman animal body which comprises administering to said body a therapeutically effective amount of a compound of the present invention.

Compounds of the invention can be administered by any suitable route, for example by oral, buccal, inhalation, sublingual, rectal, vaginal, transurethral, nasal, topical, percutaneous, i.e., transdermal, or parenteral (including intravenous, intramuscular, subcutaneous, and intracoronary) administration. Parenteral administration can be accomplished using a needle and syringe, or using a high pressure technique, like POWDERJECT™.

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Oral administration of a compound of the invention is the preferred route. Oral administration is the most convenient and avoids the disadvantages associated with other routes of administration. For patients suffering from a swallowing disorder or from impairment of drug absorption after oral administration, the drug can be administered parenterally, e.g., sublingually or buccally.

Compounds and pharmaceutical compositions suitable for use in the present invention include those wherein the active ingredient is administered in an effective amount to achieve its intended purpose. More specifically, a "therapeutically effective amount" means an amount effective to prevent development of, or to alleviate the existing symptoms of, the subject being treated. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

A "therapeutically effective dose" refers to that amount of the compound that results in achieving the desired effect. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, which is expressed as the ratio between LD₅₀ and ED₅₀. Compounds which exhibit high therapeutic indices are preferred. The data obtained from such data can be used in formulating a range of dosage

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for use in humans. The dosage of such compounds preferably lies within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage can vary within this range
5 depending upon the dosage form employed, and the route of administration utilized.

The exact formulation, route of administration, and dosage can be chosen by the individual physician in view of the patient's condition. Dosage amount and interval can be adjusted individually
10 to provide plasma levels of the active moiety which are sufficient to maintain the therapeutic effects.

The amount of composition administered is dependent on the subject being treated, the subject's weight, the severity of the affliction, the
15 manner of administration, and the judgment of the prescribing physician.

Specifically, for administration to a human in the curative or prophylactic treatment of the conditions and disorders identified above, oral
20 dosages of a compound of the present invention generally are about 0.5 to about 1000 mg daily for an average adult patient (70 kg). Thus, for a typical adult patient, individual tablets or capsules contain 0.2 to 500 mg of active compound, in a suitable
25 pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day. Dosages for intravenous, buccal, or sublingual administration typically are
30 0.1 to 500 mg per single dose as required. In practice, the physician determines the actual dosing regimen which is most suitable for an individual patient, and the dosage varies with the age, weight,

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and response of the particular patient. The above dosages are exemplary of the average case, but there can be individual instances in which higher or lower dosages are merited, and such are within the scope of this invention.

For human use, a compound of the present invention can be administered alone, but generally is administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. Pharmaceutical compositions for use in accordance with the present invention thus can be formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries that facilitate processing of compounds of the present invention into preparations which can be used pharmaceutically.

These pharmaceutical compositions can be manufactured in a conventional manner, e.g., by conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Proper formulation is dependent upon the route of administration chosen. When a therapeutically effective amount of a compound of the present invention is administered orally, the composition typically is in the form of a tablet, capsule, powder, solution, or elixir. When administered in tablet form, the composition can additionally contain a solid carrier, such as a gelatin or an adjuvant. The tablet, capsule, and powder contain about 5% to about 95% compound of the present invention, and preferably from about 25% to about 90% compound of the present

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invention. When administered in liquid form, a liquid carrier such as water, petroleum, or oils of animal or plant origin can be added. The liquid form of the composition can further contain physiological saline solution, dextrose or other saccharide solutions, or glycols. When administered in liquid form, the composition contains about 0.5% to about 90% by weight of a compound of the present invention, and preferably about 1% to about 50% of a compound of the present invention.

When a therapeutically effective amount of a compound of the present invention is administered by intravenous, cutaneous, or subcutaneous injection, the composition is in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred composition for intravenous, cutaneous, or subcutaneous injection typically contains, in addition to a compound of the present invention, an isotonic vehicle.

For oral administration, the compounds can be formulated readily by combining a compound of the present invention with pharmaceutically acceptable carriers well known in the art. Such carriers enable the present compounds to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by adding a compound of the present invention with a solid excipient, optionally grinding a resulting

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5 mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, for example, fillers and cellulose preparations. If desired, disintegrating agents can be added.

10 For administration by inhalation, compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant. In the case of a pressurized aerosol, the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges, e.g., gelatin, for
15 use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds can be formulated for parenteral administration by injection, e.g., by
20 bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, e.g., in ampules or in multidose containers, with an added preservative. The compositions can take such forms as suspensions, solutions, or emul-
25 sions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing, and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the
30 active compounds in water-soluble form. Additionally, suspensions of the active compounds can be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include

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fatty oils or synthetic fatty acid esters. Aqueous injection suspensions can contain substances which increase the viscosity of the suspension. Optionally, the suspension also can contain suitable stabilizers or agents that increase the solubility of the compounds and allow for the preparation of highly concentrated solutions. Alternatively, a present composition can be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

Compounds of the present invention also can be formulated in rectal compositions, such as suppositories or retention enemas, e.g., containing conventional suppository bases. In addition to the formulations described previously, the compounds also can be formulated as a depot preparation. Such long-acting formulations can be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

Many compounds of the present invention can be provided as salts with pharmaceutically compatible counterions. Such pharmaceutically acceptable base addition salts are those salts that retain the biological effectiveness and properties of the free acids, and that are obtained by reaction with suitable inorganic or organic bases.

In particular, a compound of the present invention can be administered orally, buccally, or

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sublingually in the form of tablets containing excipients, such as starch or lactose, or in capsules or ovules, either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. Such liquid preparations can be prepared with pharmaceutically acceptable additives, such as suspending agents. A compound also can be injected parenterally, for example, intravenously, intramuscularly, subcutaneously, or intracoronarily. For parenteral administration, the compound is best used in the form of a sterile aqueous solution which can contain other substances, for example, salts, or monosaccharides, such as mannitol or glucose, to make the solution isotonic with blood.

For veterinary use, a compound of the present invention or a nontoxic salt thereof, is administered as a suitably acceptable formulation in accordance with normal veterinary practice. The veterinarian can readily determine the dosing regimen and route of administration that is most appropriate for a particular animal.

Thus, the invention provides in a further aspect a pharmaceutical composition comprising a compound of the present invention, together with a pharmaceutically acceptable diluent or carrier therefor. There is further provided by the present invention a process of preparing a pharmaceutical composition comprising a compound of the present invention, which process comprises mixing a compound of the present invention, together with a pharmaceutically acceptable diluent or carrier therefor.

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In a particular embodiment, the invention includes a pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, or sexual arousal disorder in a female animal, including humans, comprising a compound of the present invention or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

Compounds of the present invention can be prepared by any suitable method known in the art, or by the following processes which form part of the present invention. In particular, compounds of the present invention can be prepared according to the synthetic schemes illustrated in the following examples.

It should be understood that protecting groups can be utilized in accordance with general principles of synthetic organic chemistry to provide compounds of the present invention. Protecting group-forming reagents, like benzyl chloroformate and trichloroethyl chloroformate, are well known to persons skilled in the art, for example, see T.W. Greene et al., "Protective Groups in Organic Synthesis, Third Edition," John Wiley and Sons, Inc., NY, NY (1999). These protecting groups are removed when necessary by appropriate basic, acidic, or hydrolytic conditions known to persons skilled in the art. Accordingly, compounds of the present invention not specifically exemplified herein can be prepared by persons skilled in the art.

In addition, compounds of the present invention can be converted to other compounds of the present invention. Thus, for example, a particular

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substituent can be interconverted to prepare another substituted compound of the present invention.

Examples of appropriate interconversions include, but are not limited to, OR^a to hydroxy by suitable means (e.g., using an agent such as SnCl₂ or a
5 palladium catalyst, like palladium-on-carbon), or amino to substituted amino, such as acylamino or sulphonylamino, using standard acylating or sulfonylating conditions.

10 Compounds of the present invention can be prepared as individual stereoisomers or as a racemic mixture. Individual stereoisomers of the compounds of the invention can be prepared from racemates by resolution using methods known in the art for the
15 separation of racemic mixtures into their constituent stereoisomers, for example, using HPLC on a chiral column, such as Hypersil naphthyl urea, or using separation of salts of stereoisomers. Compounds of the invention can be isolated in association with solvent molecules by crystallization from,
20 or evaporation of, an appropriate solvent.

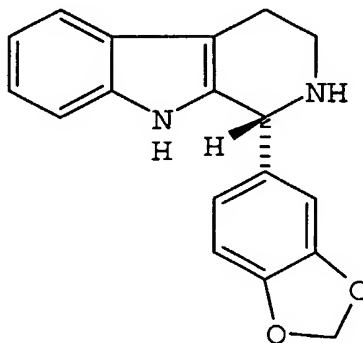
The pharmaceutically acceptable acid addition salts of the compounds of the present invention that contain a basic center can be prepared in a
25 conventional manner. For example, a solution of the free base can be treated with a suitable acid, either neat or in a suitable solution, and the resulting salt isolated either by filtration or by evaporation under vacuum of the reaction solvent.

30 Pharmaceutically acceptable base addition salts can be obtained in an analogous manner by treating a solution of a compound of the present invention with a suitable base. Both types of salt can be formed

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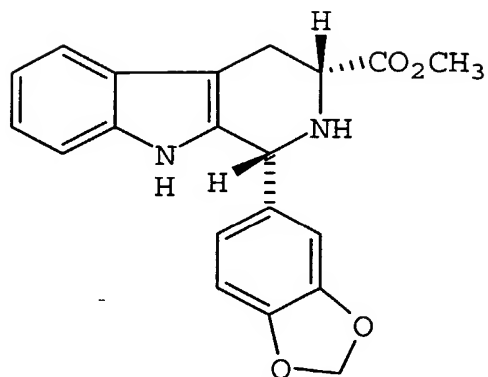
or interconverted using ion-exchange resin techniques. Thus, according to a further aspect of the invention, a method for preparing a compound of the present invention or a salt or solvate (e.g.,
5 hydrate) is provided, followed by (i) salt formation, or (ii) solvate (e.g., hydrate) formation.

Many of the following examples were prepared from the compound of structural formula (I), i.e., 1-benzo[1,3]dioxol-5-yl-2,3,4,9-tetrahydro-1H-
10 β -carboline. The synthesis of compound (I) is disclosed in Bombrun U.S. Patent No. 6,117,881, incorporated herein in its entirety by reference. Other examples were prepared from the compound of structural formula (II). The synthesis of compound (II)
15 is disclosed in Daugan U.S. Patent No. 5,859,006, incorporated herein in its entirety by reference. Compounds analogous to compounds (I) and (II), but having different substituent groups can be synthesized in an identical or similar manner as compound
20 (I) and (II) by utilizing appropriate starting materials.



(I)

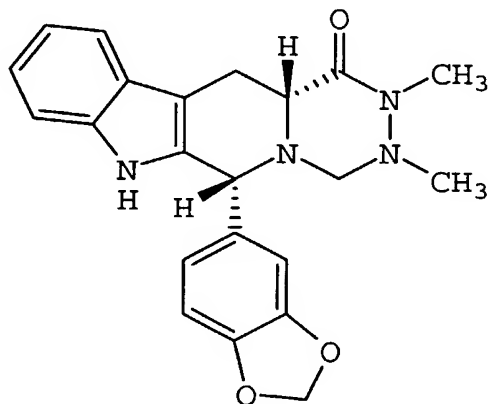
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(II)

Example 1

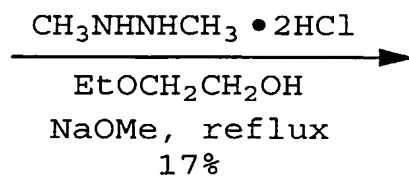
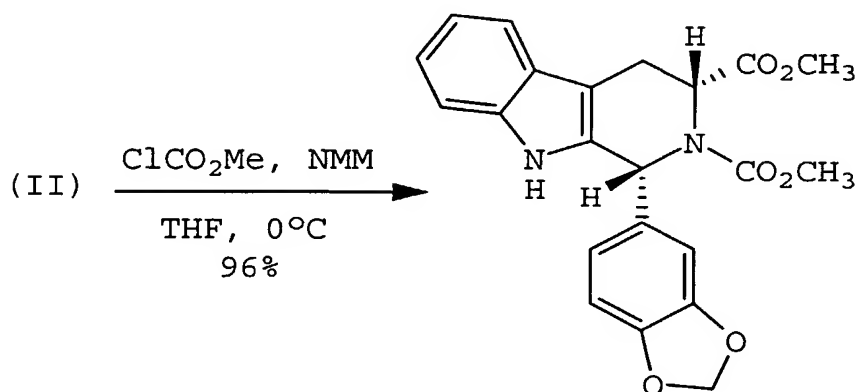
(5aR,10R) -10-Benzo[1,3]dioxol-5-yl-7,8-dimethyl-5,5a,8,9,10,11-hexahydro-7H-7,8,9a,11-tetraazabenzob[floren-6-one



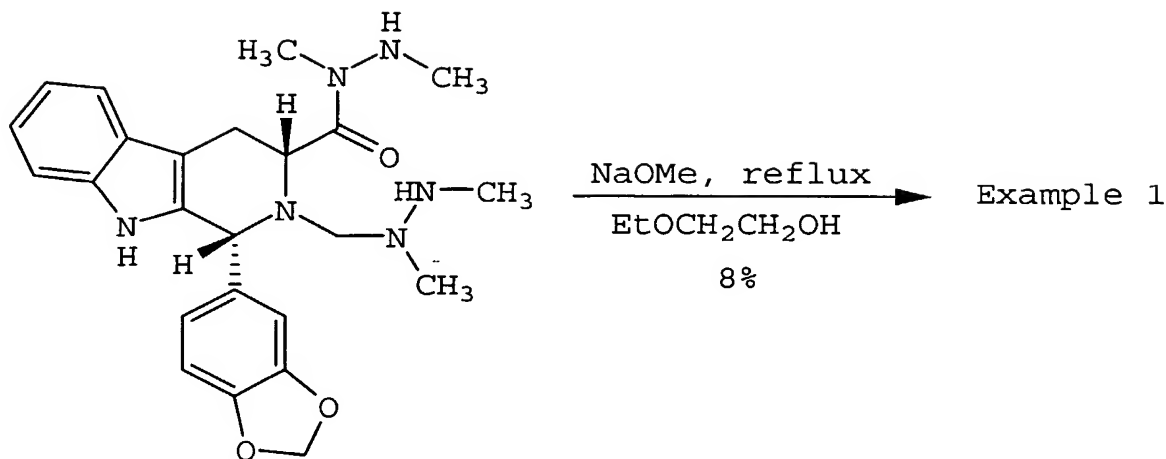
Example 1 was prepared from compound (II) using the following synthetic sequence. In general carbamate Intermediate 1 was reduced at the C4 posi-

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tion by excess hydrazine under thermal reaction conditions to provide bis-hydrazine Intermediate 2. The method of Winterfield et al. *Arch. Pharmaz*, 304, p. 216 (1971) was used to promote the cyclization of Intermediate 2 to the 2,3,5-triazine-1-one Example 1.



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Intermediate 2

**Preparation of cis- β -Carboline
Carbamate Intermediate 1**

5

Methyl chloroformate (ClCO_2Me , 4.8 mL, 62 mmol) was added dropwise to a suspension of Compound (II) (20 g, 52 mmol) and N-methylmorpholine (NMM, 14.2 mL, 129 mmol) in THF tetrahydrofuran (150 mL) at 0°C under a nitrogen blanket. The mixture was warmed slowly to room temperature, then stirred for 3 days. The resulting mixture was diluted with ethyl acetate (200 mL), washed with brine (150 mL), dried over magnesium sulfate, and filtered. The solvent was removed under reduced pressure to provide Intermediate 1 as an amber foam (21 g, 96%): TLC R_f (1:9 ethyl acetate/chloroform)=0.70. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ : 10.83 (s, 1H), 7.52 (d, $J=7.6$ Hz, 1H), 7.29 (d, $J=8.0$ Hz, 1H), 7.09 (t, $J=6.8$ Hz, 1H), 7.01 (t, $J=8.2$ Hz, 1H), 6.83 (d,

10

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J=8.1 Hz, 1H), 6.67 (s, 1H), 6.54 (d, J=8.1 Hz, 1H), 5.98 (d, J=4.2 Hz, 2H), 5.32 (d, J=5.0 Hz, 1H), 3.76 (s, 1H), 3.33 (s, 7H), 2.99-2.97 (m, 1H) ppm; API MS m/z 409 [C₂₂H₂₀N₂O₆+H]⁺.

5

**Preparation of cis-β-Carboline
Bis-Hydrazine Intermediate 2**

10 Sodium methoxide (NaOMe, 22 mL, 113 mmol, 30% solution in methanol) was added dropwise to a mixture of Intermediate 1 (14.0 g, 34 mmol) and 1,2-dimethylhydrazine dihydrochloride (9.1 g, 69 mmol) in 2-ethoxyethanol (70 mL) and the mixture was
15 heated at reflux under a nitrogen blanket for 15 hours. The suspension was cooled to room temperature, and the orange solids were removed by vacuum filtration. The filtrate was concentrated under reduced pressure to provide a dark red oil, which
20 was purified by flash column chromatography, eluting with ethyl acetate/chloroform (1:19), to provide Intermediate 2 as a yellow foam, which was used without further purification (2.62 g, 17%): TLC R_f (1:9 ethyl acetate/chloroform)=0.26; API MS m/z 351
25 [C₂₄H₃₀N₆O₃+H]⁺.

Preparation of Example 1

30 Sodium methoxide (3.2 mL, 17 mmol, 30% solution in methanol) was added dropwise to a mixture of Intermediate 2 (2.6 g, 5.6 mmol) in 2-ethoxyethanol (20 mL), then the resulting mixture was heated at reflux under a nitrogen blanket for 66 hours. The suspension was cooled to room tempera-

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ture, then concentrated under reduced pressure to provide an orange oil which was purified by flash column chromatography, eluting with ethyl acetate/-chloroform (1:19), to yield the crude product as an
5 amber foam. This residue was further purified by a slurry in water/methanol (3:1) followed by vacuum filtration to provide Example 1 as a tan powder (0.192 g, 8%): mp 207-213°C; TLC R_f (1:4 ethyl acetate/chloroform) = 0.46.

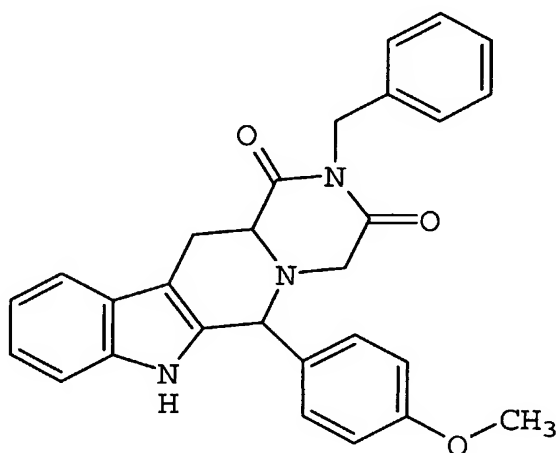
10 ^1H NMR (300 MHz, DMSO- d_6) δ : 10.22 (s, 1H), 7.45 (d, $J=7.6$ Hz, 1H), 7.19 (d, $J=7.9$ Hz, 1H), 7.00-6.88 (m, 5H), 6.02 (d, $J=7.0$ Hz, 2H), 4.65 (s, 1H), 3.77 (d, $J=11.6$ Hz, 1H), 3.50-3.46 (m, 2H), 3.34 (s, 6H), 3.22 (d, $J=14.2$ Hz, 1H), 2.78-2.70 (m, 1H) ppm; CI
15 MS m/z 391 [$\text{C}_{22}\text{H}_{22}\text{N}_4\text{O}_3 + \text{H}$] $^+$; $[\alpha]_D^{25^\circ\text{C}} = +10.0^\circ$ ($c=0.5$, chloroform). Anal. Calcd. for $\text{C}_{22}\text{H}_{22}\text{N}_4\text{O}_3 \cdot 0.25 \text{H}_2\text{O}$: C, 66.91; H, 5.74; N, 14.19. Found: C, 66.67; H, 5.66; N, 13.79. The relative stereochemistry of
20 Example 1 was confirmed to be the desired cis isomer by a several DEPT experiments, and by a series of NOE difference experiments: a positive NOE enhancement from the C12a proton at 3.77 ppm to the C6 proton at 4.65 ppm; a positive NOE enhancement from the C6 proton at 4.65 ppm to the C12a proton at 3.77
25 ppm. HPLC analysis (Aquasil C18 Column, 100 x 4.6 mm, Retention Time=12.0 minutes and 18.3 minutes; 45% acetonitrile/55% 0.03% TFA in water; flow=0.75 mL/minute; detector @ 254 nm; 25°C) showed two peaks, 6.0% of the trans isomer and 94.0% of the cis isomer, respectively, and with a total purity of
30 100%.

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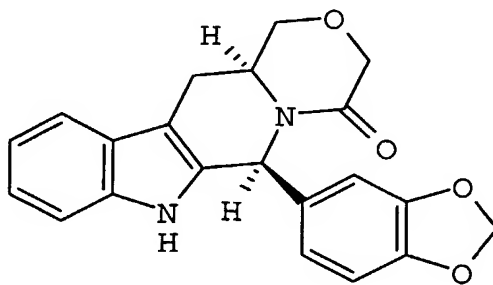
The compounds of Examples 2-23 were prepared in a manner similar to the syntheses described in Example 1 in U.S. Patent No. 5,859,006, and in U.S. Patent No. 6,117,881.

Example 2

2-Benzyl-6-(4-methoxyphenyl)-6,7,12,12a-tetrahydro-pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,3-dione

**Example 3**

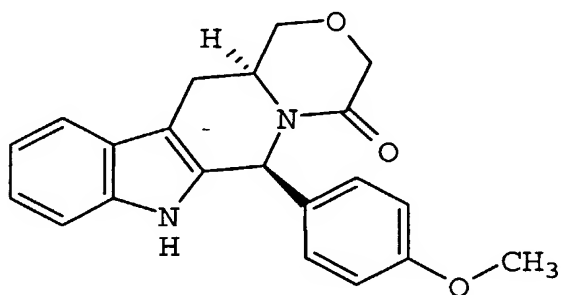
(+,-,cis)-10-Benzo[1,3]dioxol-5-yl-5a,6,10,11-tetrahydro-5H-7-oxa-9a,11-diazabenzob[b]-fluoren-9-one



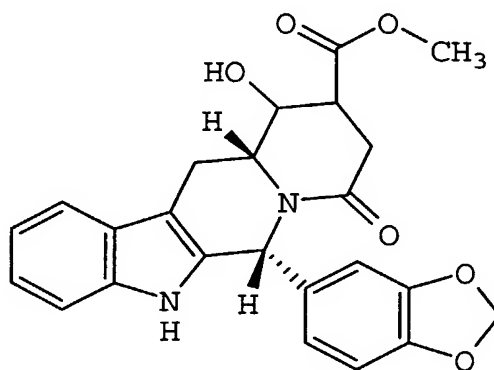
- 24 -

Example 4

(+-, cis) -10- (4-Methoxyphenyl) -5a,6,10,11-tetrahydro-5H-7-oxa-9a,11-diazabenzob[fluorene]-9-one

**Example 5**

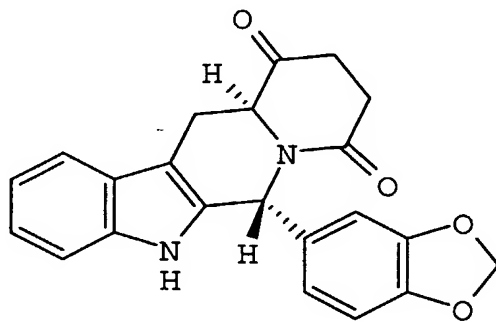
(+-, cis) -6-Benzo[1,3]dioxol-5-yl-11-hydroxy-8-oxa-5,6,8,9,11a,12-hexahydroindolo[3,2-b]-quinolizine-10-carboxylic acid methyl ester



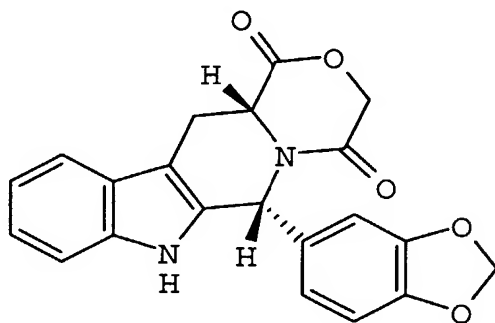
- 25 -

Example 6

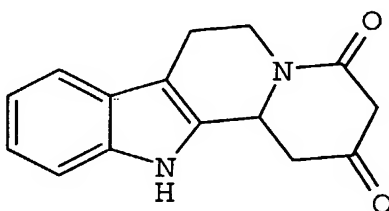
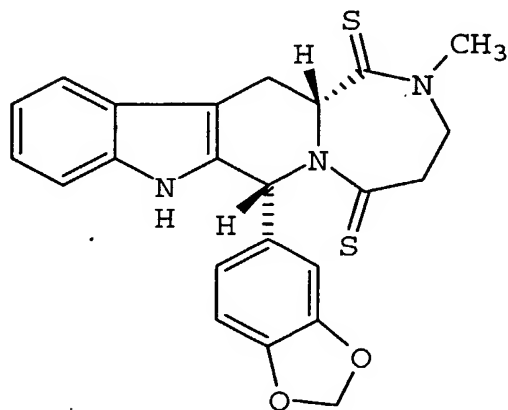
(+ -, trans) - 6 - Benzo[1,3]dioxol-5-yl-5,6,9,10,11a,12-
hexahydroindolo[3,2-b]quinolizine-8,11-dione

Example 7

(6R,11aS) - 10 - Benzo[1,3]dioxol-5-yl-5,5a,10,11-
tetrahydro-7-oxa-9a,11-diazabenzob[fluorene]-
6,9-dione



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Example 86,7,12,12b-Tetrahydro-1H-indolo[2,3-a]-
quinolizine-2,4-dioneExample 9

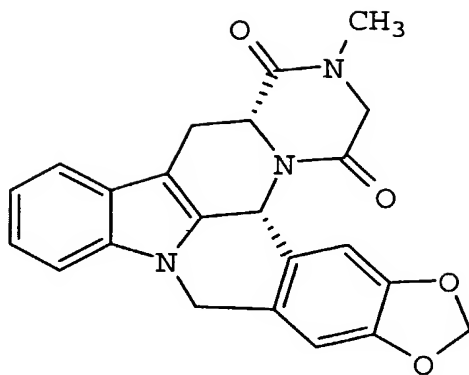
- 27 -

Example 10

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10

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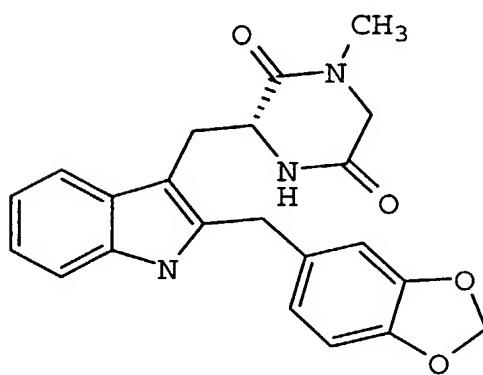
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Example 11

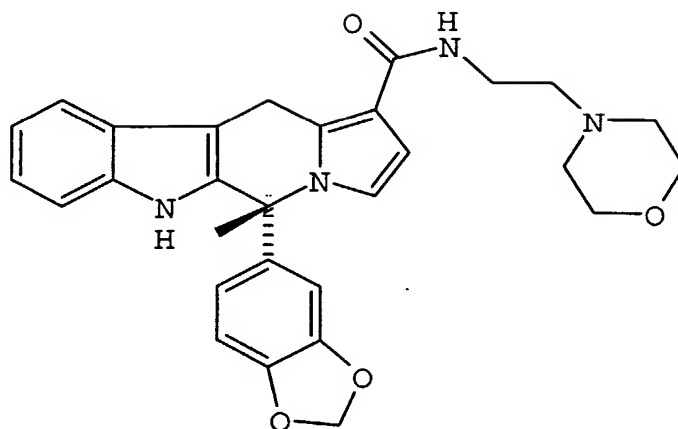
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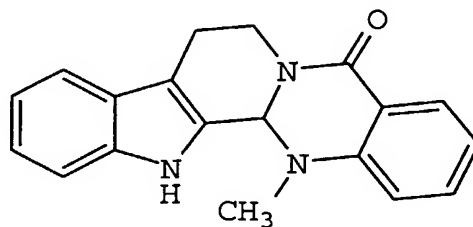
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Example 12Example 13

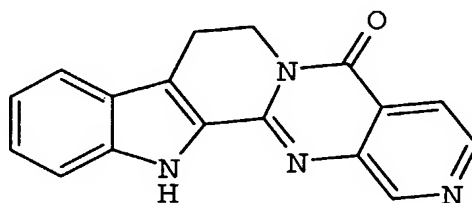
14-Methyl-8,13,13b,14-tetrahydro-7H-indolo[2',3':3,4]pyrido[2,1-b]quinazolin-5-one



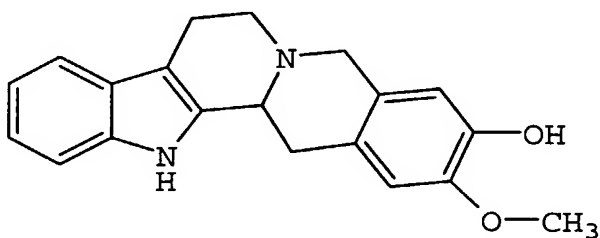
- 29 -

Example 14

5,13-Dihydro-6H-6a,10,12,13-tetraazaindeno[2,1-a]-anthracen-7-one

Example 15

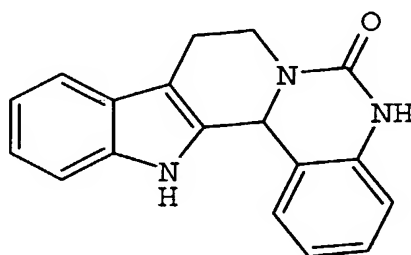
2-Methoxy-5,7,8,13,13b,14-hexahydroindolo-[2',3':3,4]pyrido[1,2-b]isoquinolin-3-ol



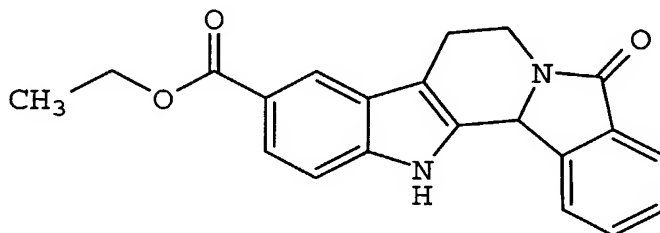
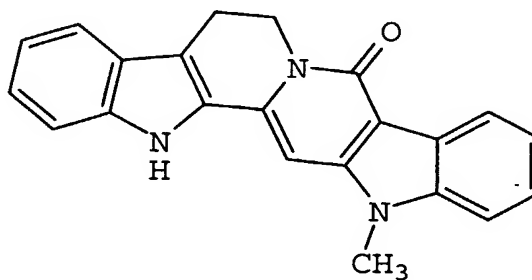
- 30 -

Example 16

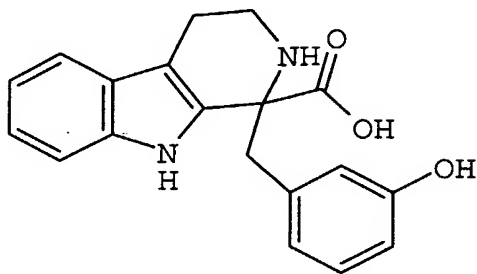
7,8,13,13b-Tetrahydro-5H-5,6a,13-triazaindeno-
[1,2-c]phenanthren-6-one

Example 17

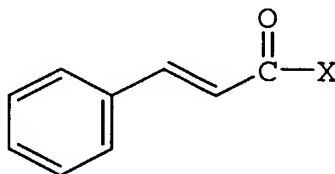
7-Oxo-5,7,11b,12-tetrahydro-6H-6a,12-diazaindeno-
[1,2-a]fluorene-3-carboxylic acid ethyl ester

Example 18

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Example 191-(3-Hydroxybenzyl)-2,3,4,9-tetrahydro-1H- β -carboline-1-carboxylic acid

The compounds of Example 20-23, and similar compounds, can be prepared from compound (I) and a compound (III).



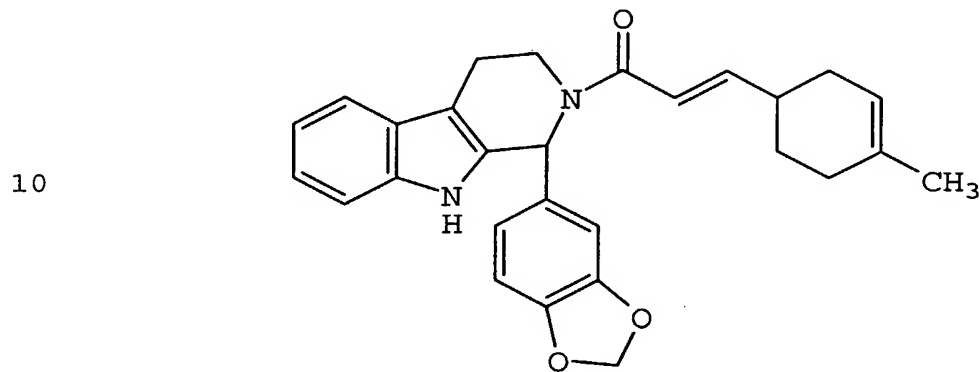
(III)

wherein X is OH or halo. The reaction is performed in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole (HOBT) in a suitable organic solvent, such as dimethylformamide (DMF) or dichloromethane (CH_2Cl_2) for several hours, e.g., 8 hours to 2 days. A heteroaryl or other aryl ring

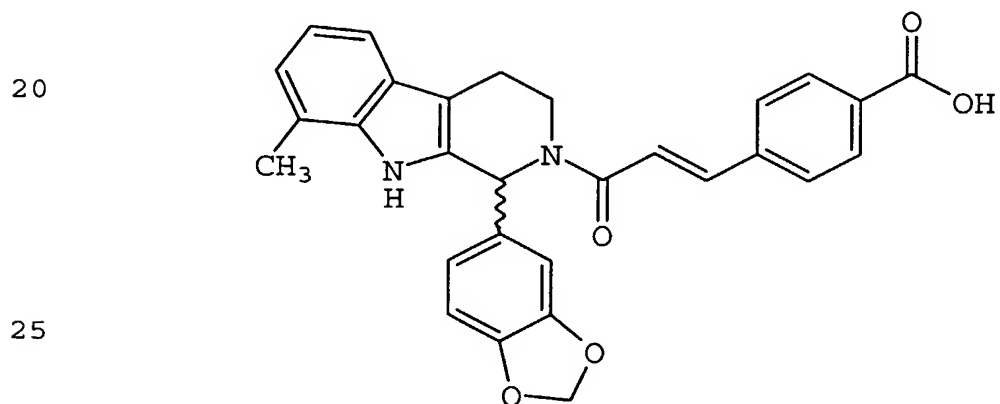
- 32 -

system can be used in place of the phenyl ring of compound (III), and the heteroaryl or aryl ring system can be optionally substituted.

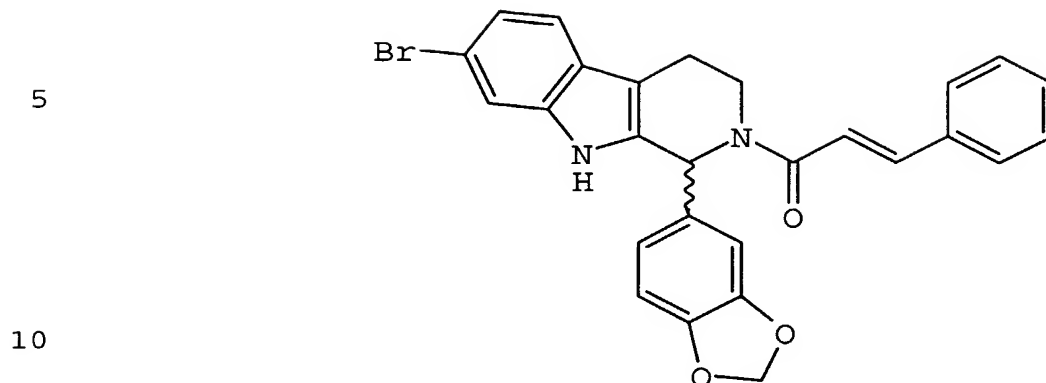
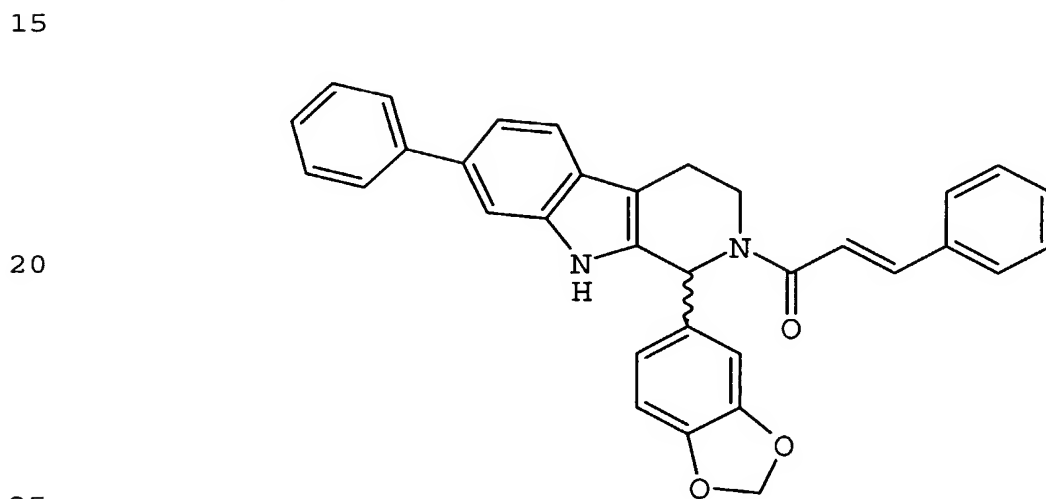
5 **Example 20**



20 **Example 21**



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Example 22Example 23

Compounds of the present invention can be formulated into tablets for oral administration.

30 For example, a compound of the present invention can be formed into a dispersion with a polymeric carrier by the coprecipitation method set forth in WO 96/38131, incorporated herein by reference. The

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coprecipitated dispersion can be blended with excipients, then pressed into tablets, which optionally are film-coated.

5 The compounds of the present invention were tested for an ability to inhibit PDE5. The ability of a compound to inhibit PDE5 activity is related to the IC_{50} value for the compound, i.e., the concentration of inhibitor required for 50% inhibition of enzyme activity. The IC_{50} value for compounds of the present invention were determined
10 using recombinant human PDE5.

 The compounds of the present invention typically exhibit an IC_{50} value against recombinant human PDE5 of less than about 50 μM , and preferably
15 less than about 25 μM , and more preferably less than about 15 μM . The compounds of the present invention typically exhibit an IC_{50} value against recombinant human PDE5 of less than about 1 μM , and often less than about 0.05 μM . To achieve the full advantage
20 of the present invention, a present PDE5 inhibitor has an IC_{50} of about 0.1 nM to about 15 μM .

 The production of recombinant human PDEs and the IC_{50} determinations can be accomplished by well-known methods in the art. Exemplary methods
25 are described as follows:

- 35 -

EXPRESSION OF HUMAN PDEs**Expression in *Saccharomyces cerevisiae* (Yeast)**

5 Recombinant production of human PDE1B,
PDE2, PDE4A, PDE4B, PDE4C, PDE4D, PDE5, and PDE7 was
carried out similarly to that described in Example 7
of U.S. Patent No. 5,702,936, incorporated herein by
reference, except that the yeast transformation vec-
10 tor employed, which is derived from the basic ADH2
plasmid described in Price et al., *Methods in*
Enzymology, 185, pp. 308-318 (1990), incorporated
yeast ADH2 promoter and terminator sequences and the
Saccharomyces cerevisiae host was the protease-defi-
15 cient strain BJ2-54 deposited on August 31, 1998
with the American Type Culture Collection, Manassas,
Virginia, under accession number ATCC 74465. Trans-
formed host cells were grown in 2X SC-leu medium, pH
6.2, with trace metals, and vitamins. After 24
20 hours, YEP medium-containing glycerol was added to a
final concentration of 2X YET/3% glycerol. Approxi-
mately 24 hr later, cells were harvested, washed,
and stored at -70°C.

HUMAN PHOSPHODIESTERASE PREPARATIONS**Phosphodiesterase Activity Determinations**

30 Phosphodiesterase activity of the prepara-
tions was determined as follows. PDE assays utiliz-
ing a charcoal separation technique were performed
essentially as described in Loughney et al. (1996).
In this assay, PDE activity converts [32P]cAMP or

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[32P]cGMP to the corresponding [32P]5'-AMP or [32P]5'-GMP in proportion to the amount of PDE activity present. The [32P]5'-AMP or [32P]5'-GMP then was quantitatively converted to free [32P]phosphate and unlabeled adenosine or guanosine by the action of snake venom 5'-nucleotidase. Hence, the amount of [32P]phosphate liberated is proportional to enzyme activity. The assay was performed at 30°C in a 100 μ L reaction mixture containing (final concentrations) 40 mM Tris HCl (pH 8.0), 1 μ M ZnSO₄, 5 mM MgCl₂, and 0.1 mg/mL bovine serum albumin (BSA). PDE enzyme was present in quantities that yield <30% total hydrolysis of substrate (linear assay conditions). The assay was initiated by addition of substrate (1 mM [32P]cAMP or cGMP), and the mixture was incubated for 12 minutes. Seventy-five (75) μ g of Crotalus atrox venom then was added, and the incubation was continued for 3 minutes (15 minutes total). The reaction was stopped by addition of 200 μ L of activated charcoal (25 mg/mL suspension in 0.1 M NaH₂PO₄, pH 4). After centrifugation (750 X g for 3 minutes) to sediment the charcoal, a sample of the supernatant was taken for radioactivity determination in a scintillation counter and the PDE activity was calculated.

Purification of PDE5 from *S. cerevisiae*

Cell pellets (29 g) were thawed on ice with an equal volume of Lysis Buffer (25 mM Tris HCl, pH 8, 5 mM MgCl₂, 0.25 mM DTT, 1 mM benzamidine, and 10 μ M ZnSO₄). Cells were lysed in a Microfluidizer[®] (Microfluidics Corp.) using nitrogen at 20,000

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psi. The lysate was centrifuged and filtered through 0.45 μ m disposable filters. The filtrate was applied to a 150 mL column of Q SEPHAROSE[®] Fast-Flow (Pharmacia). The column was washed with 1.5
5 volumes of Buffer A (20 mM Bis-Tris Propane, pH 6.8, 1 mM MgCl₂, 0.25 mM DTT, 10 μ M ZnSO₄) and eluted with a step gradient of 125 mM NaCl in Buffer A followed by a linear gradient of 125-1000 mM NaCl in Buffer A. Active fractions from the linear gradient were
10 applied to a 180 mL hydroxyapatite column in Buffer B (20 mM Bis-Tris Propane (pH 6.8), 1 mM MgCl₂, 0.25 mM DTT, 10 μ M ZnSO₄, and 250 mM KCl). After loading, the column was washed with 2 volumes of Buffer B and eluted with a linear gradient of 0-125 mM
15 potassium phosphate in Buffer B. Active fractions were pooled, precipitated with 60% ammonium sulfate, and resuspended in Buffer C (20 mM Bis-Tris Propane, pH 6.8, 125 mM NaCl, 0.5 mM DTT, and 10 μ M ZnSO₄). The pool was applied to a 140 mL column of SEPHA-
20 CRYL[®] S-300 HR and eluted with Buffer C. Active fractions were diluted to 50% glycerol and stored at -20°C.

The resultant preparations were about 85% pure by SDS-PAGE. These preparations had specific
25 activities of about 3 μ mol cGMP hydrolyzed per minute per milligram protein.

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Inhibitory Effect on cGMP-PDE

cGMP-PDE activity of compounds of the present invention was measured using a one-step assay adapted from Wells et al., *Biochim. Biophys. Acta*, 384, 430 (1975). The reaction medium contained 50 mM Tris-HCl, pH 7.5, 5 mM magnesium acetate, 250 μ g/ml 5'-Nucleotidase, 1 mM EGTA, and 0.15 μ M 8-[H³]-cGMP. Unless otherwise indicated, the enzyme used was a human recombinant PDE5 (ICOS Corp., Bothell, Washington).

Compounds of the invention were dissolved in DMSO finally present at 2% in the assay. The incubation time was 30 minutes during which the total substrate conversion did not exceed 30%.

The IC₅₀ values for the compounds examined were determined from concentration-response curves typically using concentrations ranging from 10 nM to 10 μ M. Tests against other PDE enzymes using standard methodology showed that compounds of the invention are selective for the cGMP-specific PDE enzyme.

Biological Data

The compounds according to the present invention were typically found to exhibit an IC₅₀ value of less than 500 nM (i.e., 0.5 μ M). *In vitro* test data for representative compounds of the invention is given in the following table:

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Table 1: In vitro Results	
Example	PDE5 IC ₅₀ (μ M)
1	0.093
2 ¹⁾	0.34
3	0.07
4	0.3
5	0.08
6	0.55
7	0.05
8 ¹⁾	0.25
13 ¹⁾	1
15 ¹⁾	0.3
16 ¹⁾	0.9
17 ¹⁾	1
18 ¹⁾	0.07
19	1
20	0.18
21	0.003
22	0.026
23	0.69

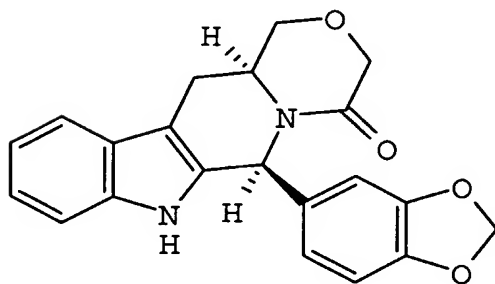
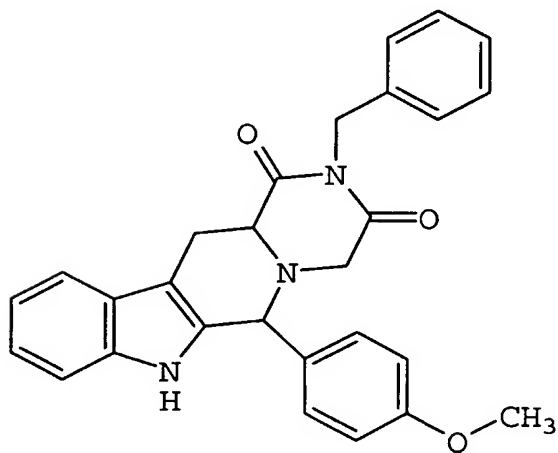
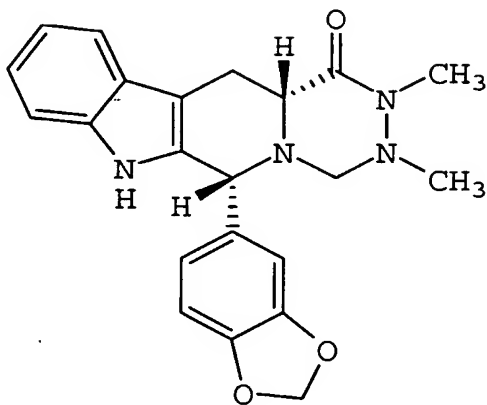
¹⁾ vs. bovine aorta

Obviously, many modifications and variations of the invention as hereinbefore set forth can be made without departing from the spirit and scope thereof, and, therefore, only such limitations should be imposed as are indicated by the appended claims.

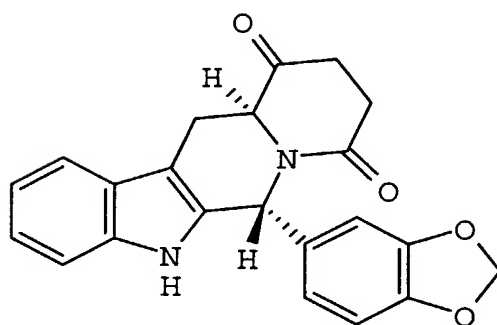
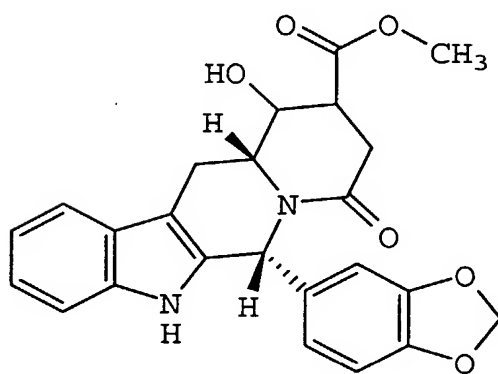
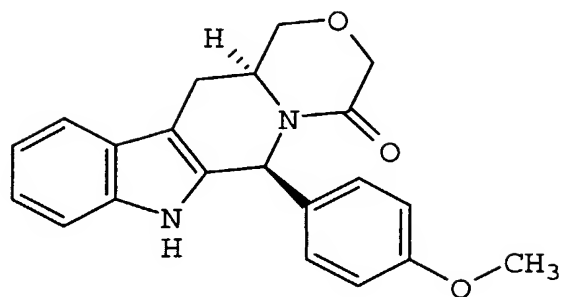
- 40 -

WHAT IS CLAIMED IS:

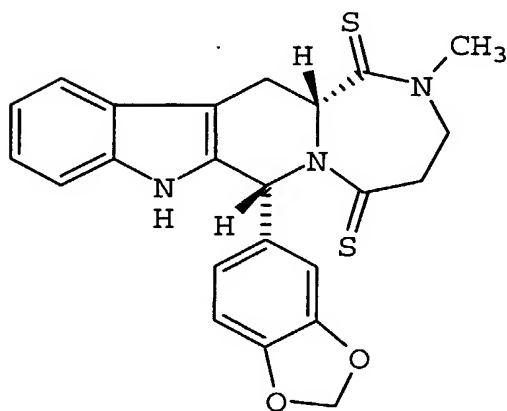
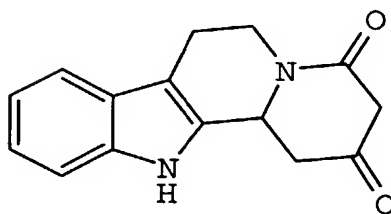
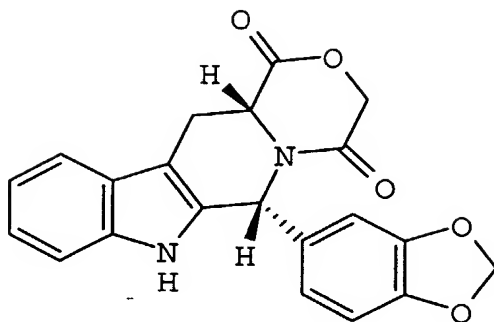
1. A compound selected from the group consisting of



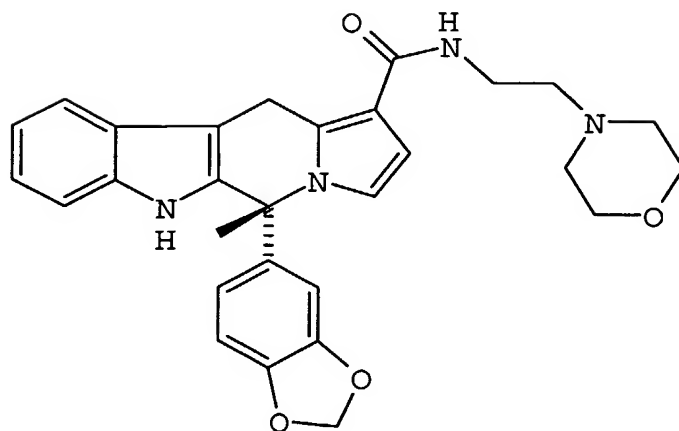
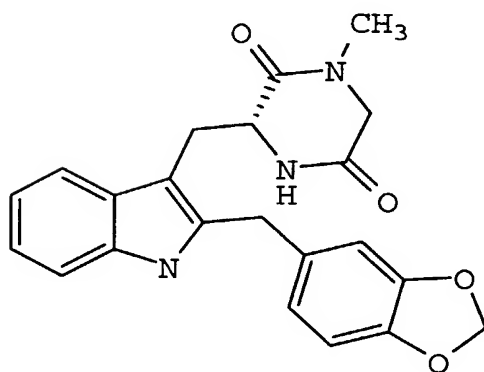
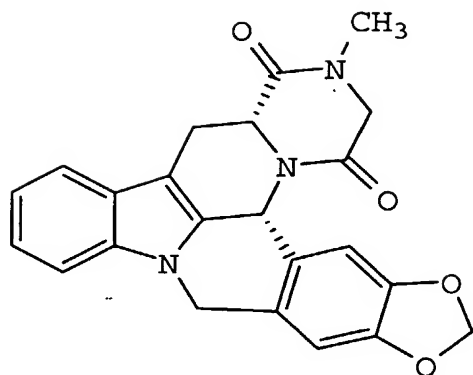
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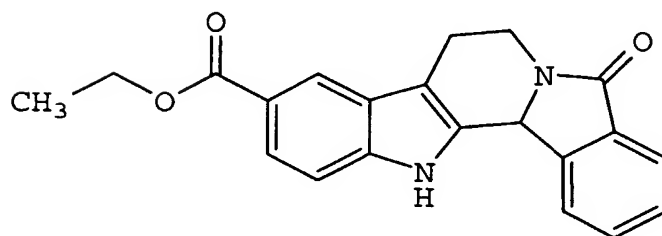
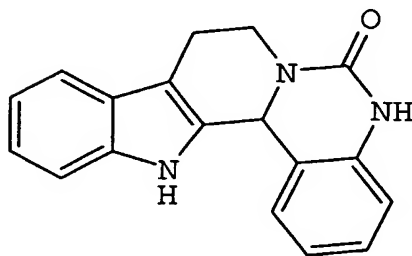
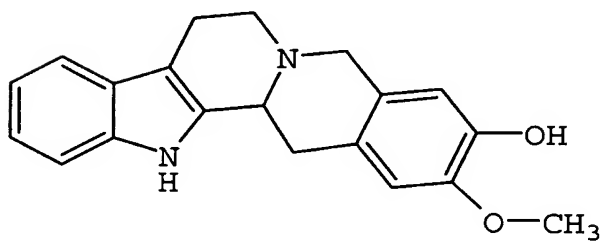
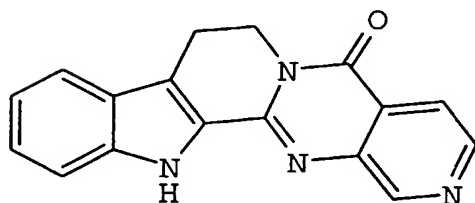
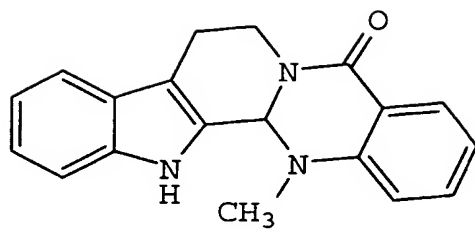
- 42 -



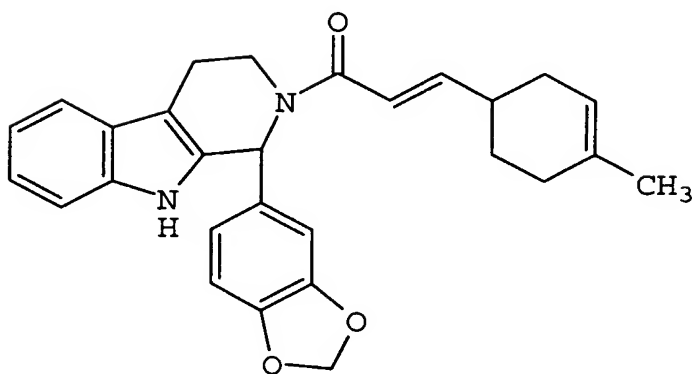
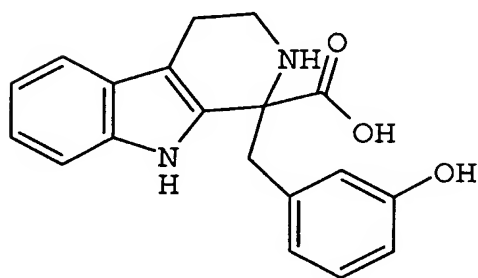
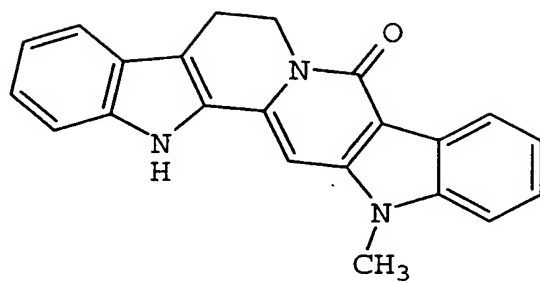
- 43 -



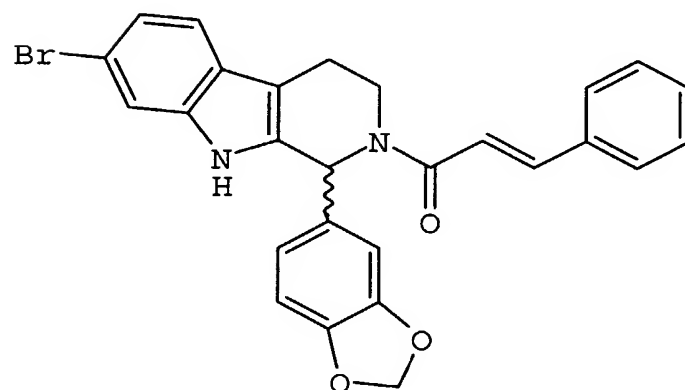
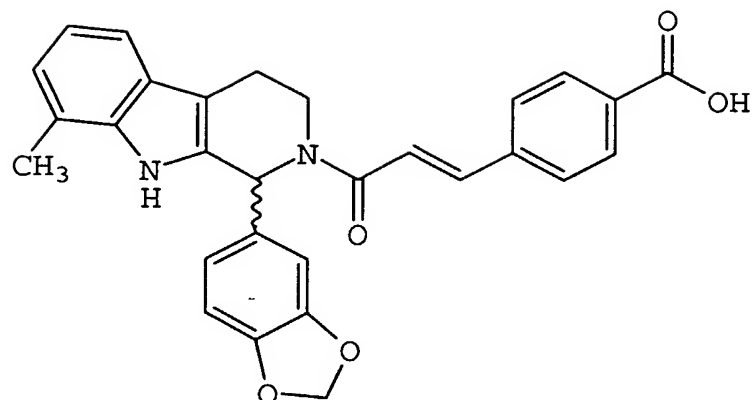
- 44 -



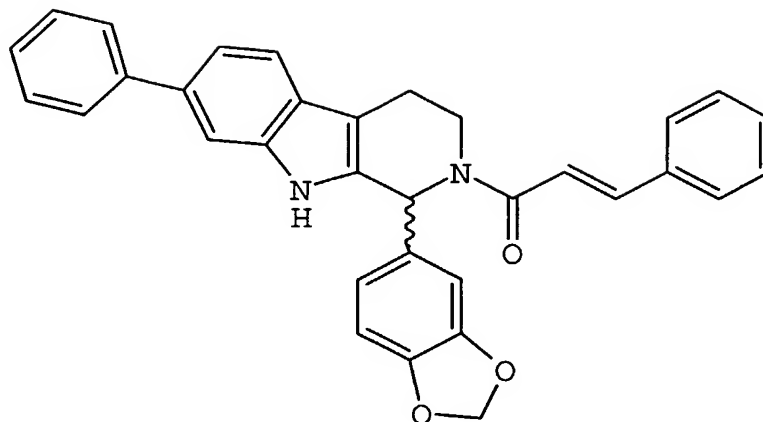
- 45 -



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2. A pharmaceutical composition comprising a compound of claim 1, together with a pharmaceutically acceptable diluent or carrier.

3. A method of treating a male or female animal in the treatment of a condition where inhibition of a cGMP-specific PDE is of a therapeutic benefit comprising treating said animal with an effective amount of a pharmaceutical composition comprising a compound of claim 1, together with a pharmaceutically acceptable diluent or carrier.

4. The method of claim 3 wherein the condition is male erectile dysfunction.

5. The method of claim 4 wherein the treatment is an oral treatment.

6. The method of claim 3 wherein the condition is female arousal disorder.

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7. The method of claim 6 wherein the treatment is an oral treatment.

8. The method of claim 3 wherein the condition is selected from the group consisting of stable angina, unstable angina, variant angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, malignant hypertension, pheochromocytoma, acute respiratory distress syndrome, congestive heart failure, acute renal failure, chronic renal failure, atherosclerosis, a condition of reduced blood vessel patency, a peripheral vascular disease, a vascular disorder, thrombocythemia, an inflammatory disease, myocardial infarction, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, peptic ulcer, a gut motility disorder, postpercutaneous transluminal coronary angioplasty, carotid angioplasty, post-bypass surgery graft stenosis, osteoporosis, preterm labor, benign prostatic hypertrophy, and irritable bowel syndrome.

9. A method of treating a condition where inhibition of a cGMP-specific PDE is of therapeutic benefit, in a human or a nonhuman animal body, comprising administering to said body a therapeutically effective amount of a compound of claim 1.

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10. A method for the curative or prophylactic treatment of male erectile dysfunction or female arousal disorder, comprising administration of an effective dose of a compound of claim 1, and pharmaceutically acceptable salts and solvates thereof, to an animal.

11. Use of a compound of claim 1 for the manufacture of a medicament for the curative or prophylactic treatment of a condition where inhibition of a cGMP-specific PDE is of a therapeutic benefit.

INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/US 02/13719

A. CLASSIFICATION OF SUBJECT MATTER

 IPC 7 C07D471/14 C07D498/14 C07D405/06 A61K31/5025 A61K31/4985
 A61K31/436 A61K31/473 A61P9/00 A61P15/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	W0 01 94347 A (LILLY ICOS LLC) 13 December 2001 (2001-12-13) the whole document ----	1-11
P,A	W0 02 28859 A (LILLY ICOS LLC) 11 April 2002 (2002-04-11) page 68 -page 101; claims 1-29 ----	1-11
P,A	W0 01 87038 A (ORTHO-MCNEIL PHARMACEUTICAL) 22 November 2001 (2001-11-22) page 67 -page 154; claims 1-27 ----	1-11
Y	W0 00 15639 A (ICOS CORPORATION) 23 March 2000 (2000-03-23) page 67 -page 81; claims 1-34 ----- -/--	1-11

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

20 September 2002

Date of mailing of the international search report

01/10/2002

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INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 43287 A (ICOS CORPORATION) 20 November 1997 (1997-11-20) page 116 -page 119; claims 1,2 ---	1-11
Y	WO 97 03985 A (LABORATOIRE GLAXO WELLCOME S.A) 6 February 1997 (1997-02-06) page 18 -page 20; claims 1-13 ---	1-11
Y	WO 95 19978 A (LABORATOIRE GLAXO WELLCOME S.A) 27 July 1995 (1995-07-27) page 78 -page 83; claims 1-16 ---	1-11
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A	US 5 747 520 A (YVES POMMIER ET AL.) 5 May 1998 (1998-05-05) the whole document ---	1-11
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Y	EDMUND SYBETZ ET AL.: "Inhibitors of PDE1 and PDE5 cGMP phosphodiesterases: patents and therapeutic potential" EXPERT OPINION ON THERAPEUTIC PATENTS., vol. 7, no. 6, 1997, pages 631-639, XP002178692 ASHLEY PUBLICATIONS., GB ISSN: 1354-3776 the whole document -----	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/13719

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 3-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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Information on patent family members

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